HIGH FIBER DIET AND COLON CANCER: A CRITICAL REVIEW

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INTRODUCTION

Epidemiologic studies have not provided a clear
answer to the question of whether a diet rich in fiber (or
nutrients/micronutrients associated with such a diet) can
reduce the risk of colon cancer. The inconsistency of
study results reflects, to some degree, variation in
populations studied, dietary measures, and methods
employed. Several recent publications have examined the
impact that methodologic problems can have on observed
results in analytical epidemiologic studies (Byar and
Freedman, in press; Prentice et al., 1989; Willett, 1989).
However, methodologic considerations have largely been
ignored in previous reviews of the relationship between
colon cancer and fiber-rich diets (Bingham 1986; McKeown-
Eyssen, 1987; Greenwald et al., 1987). To determine the
level of support in the epidemiologic literature for colon
cancer risk modification by such diets, a critical review
was undertaken that focused on adequacy of methods as well
as research results. This paper will consider case-
control studies published in English during the years
1973–1988 (see Trock et al., in press; for a more
comprehensive review that includes studies other than
case-control).

METHODS

A total of 23 epidemiologic studies that examined the association between colon cancer risk and diets high in vegetables, fruits, grains, and fiber were identified through Index Medicus and the bibliographies of identified papers. Case-control studies were emphasized because they were the most numerous and methodologically rigorous among the body of epidemiologic studies. Only the published data were analyzed; odds ratios, confidence intervals or study power were calculated by the author if omitted from the published manuscript.

This review included studies that used any measure of dietary intake whose rank values could reasonably be expected to discriminate between high and low levels of dietary fiber intake. Thus, studies that used quantitative estimates of crude, dietary or total fiber, specific fiber components, or frequency of consuming vegetables or high-fiber foods were all considered. It should be noted that all such measures are subject to random and systematic errors to varying degrees (Willett, 1989), and "quantitative" measures of fiber do not necessarily estimate "true" long-term fiber intake more accurately than simple food frequency measures (Prentice et al., 1989).

Study methodology was evaluated to determine the extent to which the observed study results may have been influenced by confounding and other forms of bias, study power, and adequacy of exposure data. Based on this assessment and the observed value of the effect measure, the strength of the evidence for a protective effect was derived for each study. For each study, the evidence for an inverse association between colon cancer risk and dietary intake was classified as being strong, moderate, equivocal, or strongly lacking. The criteria for these classifications are as follows:

Strong evidence: a) inverse association between colon cancer risk and dietary vegetable, fruit, grain or fiber intake is statistically significant; b) effect remains significant after adjustment for confounding factors (or no significant potential confounders demonstrated); c) no apparent sources of bias or other methodologic weakness which would explain observed effect as an artifact.

Moderate evidence: a) crude (unadjusted) inverse association between fiber-rich diet and colon cancer risk is statistically significant; b) no adjustment for potential confounders performed; c) no other apparent methodologic weaknesses or source of spurious effect.

Equivocal evidence: a) association between colon cancer risk and fiber-rich diet is non-significant or becomes so after adjustment; or b) effects of fiber-rich diet cannot be discriminated from other correlated dietary constituents that are also associated with colon cancer risk (e.g. fats, calories); or c) obvious sources of bias or methodologic weakness.

Strongly lacking evidence: a) no statistically significant inverse association between colon cancer risk and fiber-rich diet; b) no apparent sources of bias, methodologic weakness, or evidence of significant non-differential error effect.

In addition to classifying the level of support of each study, a meta-analysis of the case-control studies was performed. A summary odds ratio (OR) estimate was calculated as the variance-weighted average of the individual log-odds ratios (Fleiss, 1981). For each study, the OR reflected a comparison between highest and lowest intake quantiles for the most relevant measure of fiber intake. Adjusted OR were used whenever the published data allowed for estimation of the variance of the log-odds ratio; otherwise crude OR were used. Despite variation in measures of exposure, it was felt that a summary OR estimate based on extreme quantiles of intake would combine reasonably comparable high and low fiber intake groups across studies.

RESULTS

Table 1 shows classification of the 23 case-control studies according to strength of evidence, and provides some details of the observed results and methodological assessment (for more detail, see Trock et al., in press). Note that studies showing only a crude OR but classified as "Strong Evidence" were those that did not find

significant effects of confounders. Furthermore, several studies were classified as equivocal because risk estimates were based on single foods, and/or both excess risk and protective effects were observed in different foods associated with fiber.

Table 1.   Strength of Evidence from Case-Control Studies of
         High Fiber Diet and Colon Cancer

First Author (year)	Odds Ratio (95% c.i.)	Adjusted Effect (Y/N)	Methodologic Considerations
I. STRONG EVIDENCE			
Graham (1978)	0.47* (.22, .99)	N	V
Manousos (1983)	0.32** (-)	Y	V
Tuyns (1986)	0.62** (.58,.75)	N	DF; similar V effect
Macquart-Moulin (1986)	0.54*** (.36,.80)	N	VF
Kune (1987)	0.44*** (-)	Y	TF (M); similar V effect
	0.35*** (-)	Y	TF (F); similar V effect
Young (1988)	0.53* (.37,.76)	Y	Lettuce salad
Slattery (1988)	0.4* (.2,.8)	Y	CF (M); similar V effect
	0.5 (.2,1.1)	Y	CF (F); similar V effect
La Vecchia (1988)	0.5** (-)	Y	Green V
Graham (1988)	0.58 (.28,1.2)	Y	DF (M); signif. trend
	0.44* (.20,.97)	Y	DF (F)
II. MODERATE EVIDENCE			
Bjelke (1974)	0.76 (-)	N	V; CF also protects
Modan (1975)	0.70* (-)	N	HFI; OR imputed
Dales (1978)	0.50 (-)	Y	HFI
Bristol (1985)	0.33* (.1,1.0)	N	DF
Lyon (1987)	0.8 (-)	Y	CF (M)
	0.6 (-)	Y	CF (F)
Tuyns (1988)	0.37*** (-)	N	V
III. EQUIVOCAL EVIDENCE			
Haenszel (1973)	2.3** (-)	Y	Single V; some V protect
Phillips (1975)	0.5 (.15,1.7)	N	Green leafy V; low power, narrow fiber distribution
Haenszel (1980)	0.76* (.59,.98)	N	Single V; some V protect
Martinez (1981)	1.5 (.9,2.6)	N	HFI; narrow fiber distribution
Pickle (1984)	1.77 (-)	N	HFI; cruciferous V and grain protect in subgroup
Tajima (1985)	0.88 (-)	N	Single V; excess risk for some V
IV. STRONGLY LACKING EVIDENCE			
Miller (1983)	0.9 (-)	Y	DF (M)
	1.2 (-)	Y	DF (F)
Potter (1986)	1.1 (0.5,2.4)	Y	DF/MJ energy intake (M)
	2.0 (0.8,5.0)	Y	DF/MJ energy intake (F)

$*$ = p<.05; $**$ = p<.01; $***$ = p<.001; (-) = 95% c.i. not available
V=vegetables; DF=dietary fiber; TF=total fiber; CF=crude fiber;
OR=odds ratio; M=males; F=females; HFI=high fiber index; MJ=millijoule

Table 1 shows that 15 studies exhibit evidence that either strongly or moderately supports an inverse association between high fiber diet and risk, while only 8 studies provide equivocal or no evidence for protection. Furthermore, of the 6 equivocal studies, 2 were at least consistent with a protective effect, even if the association was not significant, or employed a questionable exposure measure.

Failure to adjust for confounding nutrients may have had only a minor effect on evidence from studies classified as "moderate." Among studies that did adjust, 5 exhibited little or no change in the observed effect, 4 exhibited an enhanced protective effect, 1 exhibited a reduced protective effect, and 2 exhibited no change for males, and a reduced effect for females (one of which was reduction of an apparent excess risk). This is relevant because high correlations between fiber intake and other nutrients can diminish the power to detect a significant fiber effect when adjusting by multivariable methods (Byar and Freedman, in press). Thus, the lack of appreciable reduction in effect following adjustment indicates that such Type II had only minimal influence on the observed results.

It has been suggested that analytic epidemiologic data from studies based on vegetable intake is more compelling than that from studies which have estimated fiber intake (NAS, 1989; Potter, in press). It is unlikely that current retrospective dietary data can actually discriminate between the separate influences of non-fiber components of vegetables and fiber per se. In Western countries, people who consume large amounts of fiber are most likely to consume high levels of vegetables in the process; conversely those with high vegetable intake will achieve high fiber intake (Block and Lanza, 1987).

Thirteen case-control studies assessed risks associated with measures of fiber, and 13 assessed risk associated with vegetable intake frequency (three studies used both types of measures and are counted twice). Studies based on vegetable intake included 7 classified as strong evidence, 2 moderate, and 4 equivocal. Studies based on fiber included 5 classified as strong, 4

moderate, 2 equivocal, and 2 strongly lacking evidence for a protective effect. Thus, although the evidence is somewhat more consistent for vegetable-based risk estimates, it does not suggest that available data are unsupportive of protection in studies based on fiber intake.

Risk modification resulting from vitamin or micronutrient contents of a diet high in fruits and vegetables has been suggested as an alternative to a protective effect of fiber. Although not examined in the same level of detail as fiber and vegetables in this review, the results are less supportive of this hypothesis. Only 4 of 12 studies examining associations with fruit found protective effects; 3 of 7 studies found protective effects associated with estimated vitamin C intake; 2 of 6 studies found reduced risk associated with estimated beta-carotene intake.

Meta Analysis Results

Sixteen of the 23 studies provided sufficient data in the published report to permit inclusion in a meta-analysis which gave a summary odds ratio (data to calculate variances of individual log-odds ratios were required for inclusion). Odds ratios comparing highest to lowest quantile of intake were used; adjusted OR were used whenever sufficient data were present, otherwise crude OR were used (however, in only 2 cases did the crude OR that was used differ substantially from the adjusted; this resulted in use of 1 estimate that was more protective than the adjusted, and 1 estimate that was less protective). The seven studies not included in the meta-analysis were Bjelke; Modan et al; Pickle et al.; Tajima and Tominaga; Lyon et al.; La Vecchia et al.; and Tuyns et al. 1988. When sex specific odds ratios were given for a study, both were entered separately in the meta-analysis. Table 2 presents results for all 16 studies combined, 10 studies based on fiber intake, and 9 studies based on vegetable intake.

Table 2. Meta-analysis of Case-Control Data for
          Effects of Fiber and Vegetables.

COMBINED ANALYSIS

a. 16 studies:

    Heterogeneity χ^2 = 65.9 (20 df); p < .001

b. 12 studies (4 equivocal studies excluded):

    Heterogeneity χ^2 = 21.7 (16 df); p=.16

    Combined OR (95% c.i.) = 0.57 (0.50, 0.64)

STUDIES BASED ON FIBER ESTIMATES

a. 10 studies:

    Heterogeneity χ^2 = 32.4 (14 df); p < .005

b. 9 studies (1 equivocal study excluded):

    Heterogeneity χ^2 = 19.2 (13 df); p=.11

    Combined OR (95% c.i.) = 0.58 (0.51, 0.66)

STUDIES BASED ON VEGETABLE INTAKE FREQUENCY

a. 9 studies:

    Heterogeneity χ^2 = 43.0 (10 df); p < .0001

b. 6 studies (3 equivocal studies excluded):

    Heterogeneity χ^2 = 3.7 (7df); p > .75

    Combined OR (95% c.i.) = 0.48 (0.41, 0.57)

The meta-analyses are in good agreement with the results of the qualitative analysis, and indicate a reduction in risk of approximately 40% associated with high intake of fiber or vegetables. The relatively small difference between the studies based on fiber estimates and those based on vegetable frequency also accords well with the qualitative analysis. The justification for the exclusion of equivocal studies is that the influence of bias or exposure misclassification on the observed study

result could not be ruled out, leading to effect measures of questionable validity or precision. It should be noted that the four equivocal studies included two with OR > 1 and two with OR < 1. It is also worth noting that some of the heterogeneity of effect is due to variation among studies which all exhibited protective effects; the range of OR in such studies was 0.3-0.7.

The seven studies that lacked sufficient data to be included in the meta-analysis cannot be assumed to represent a random sample of case-control studies. To determine whether the meta-analysis results could have been biased by the exclusion of these studies, an ad hoc method of estimating the variance of the log-odds ratio was developed, which required only the OR estimate and the total number of cases and controls. This method was first validated on studies which <u>did</u> have sufficient data for variance estimation, and it was found that the ad hoc variances were very good approximations of the sample variances. The ad hoc variance would only be likely to be significantly biased if one or more cells in the cross-classification of disease and exposure contained small numbers of cases or controls. Using this approach, it was found that the seven excluded studies yielded a combined OR = 0.58 (see Trock et al., in press for more details). Thus it is likely that the meta-analysis results would have been little changed by inclusion of the seven studies.

DISCUSSION

Critical evaluation of data from case-control studies produced considerable support for colon cancer risk reduction associated with diets high in grains and vegetables. Yet, analytical epidemiologic studies are susceptible to bias from a number of sources, including recall problems, difficulties in measuring and estimating nutrient intake, and correlations between nutrients. However, the most likely impact of these sources of error is a non-differential misclassification, resulting in some degree of underestimation of the true population effect parameter (Willett, 1989; Byar and Freedman, in press).

The types of errors described are less likely to produce a spurious protective effect of fiber-rich diets. Kupper has described how measurement errors in confounding variables can produce either differential or non-differential misclassification when adjusting with multi-variable methods (Kupper, 1984). However, if the protective effects observed in the studies reviewed above were the result of such errors, then one would expect to see large differences between crude and adjusted odds ratios; such differences were not observed. Furthermore, differential recall between cases and controls is unlikely to have produced the observed risk reduction as an artifact because large differences in recall are required to produce spurious deviation from the null hypothesis (Marshall et al., 1980).

A variety of nutrient intake measures have been used in the studies reviewed here. Variation exists across studies in terms of the specific foods that were included in fiber indices, whether questionnaires elicited amount as well as frequency of intake, and the databases used to convert dietary intake to nutrient values (Potter, in press). Despite this lack of precision, it is not at all apparent that these measures are inadequate for inducing an ordering among study subjects (Willett et al., 1985). Therefore, the assumption that most exposure indicators were sufficiently comparable to allow discrimination between extremes of fiber intake appears to be tenable.

The measurement problems discussed above do limit the precision of inferences which may be drawn from the analytical studies. Although these measures are adequate for rank ordering of nutrient intake, they vary considerably in the accuracy with which they estimate specific nutrient intake values in individuals. This lack of precision, coupled with the high proportion of dietary fiber derived from vegetables in most Western diets, makes it unlikely that retrospective dietary data will permit resolution of the fiber and non-fiber effects of a diet rich in grains and vegetables.

In summary, the analytic epidemiologic data strongly support a reduction in colon cancer risk of approximately 40% among individuals consuming diets with high vegetable and grain content. Associations with fruit, vitamin C and

beta-carotene appear much less consistent, suggesting that
protection is unlikely to be conferred by micronutrients.
The observed results appear extremely unlikely to be due
to artifact arising from measurement error or other
sources of bias. Nevertheless, the limitations of current
data and the probable interactions between fiber, other
nutrients and endogenous processes make it impossible for
existing analytic studies to identify the specific
component(s) of a high fiber diet that confers protection.
Clinical trials, such as the recent polyp trial (Decosse
et al., 1989), and research tools that are more sensitive
to the complexity of the epidemiology of diet and cancer
will be required to characterize the protective agent(s)
more precisely.

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